

REMARKS

Status of Claims

By this Amendment, Claims 20, 24, 26-28, 33, 34, 36, and 39-42 are amended. Claims 20-42 are pending in this application.

Claims 20 and 33 have been amended to recite an “optically pure” cyanohydrin. Support for this amendment can be found, for example, on page 3, paragraph 8, and page 17, paragraph 3, of the specification. Claims 20 and 33 have been further amended by replacing the phrase “in a reaction mixture comprising” with “comprising, combining in a reaction mixture”.

In Claim 24, the phrase “ranges from 1.5 equivalents to” has been replaced with the phrase “is less than”. Support for the use of less than 10 equivalents of mineral acid relative to the optically active cyanohydrin can be found, for example, on page 44, paragraph 2, of the specification.

In Claims 26 and 33, the term “boracic” has been replaced with the term “boric”. According to Webster’s II New College Dictionary, “boracic” is a variation of the term “boric”. (page 128, (2001)). Also, Claims 26 and 33 have been amended to recite “nitric acid” which was inadvertently omitted. Support for nitric acid can be found, for example, on page 44, paragraph 3, of the specification.

In Claims 27 and 28, each occurrence of the term “comprising” has been replaced with the phrase “consisting essentially of” to recite the number of carbon atoms forming the hydrocarbon.

Claims 34 and 39-42 have been amended to recite an optically “pure” α -hydroxycarboxylic acid. Support for this amendment can be found, for example, on page 3, paragraph 8, and page 17, paragraph 3, of the specification.

In Claim 36, the term “comprises” has been replaced with the phrase “is selected from” to properly recite the element of at least one hydrocarbon solvent.

Thus, Applicants respectfully submit that no question of new matter arises, and entry of this amendment is, therefore, respectfully requested.

Objection

The Office objects to the spelling of the term “boracic” in Claim 26. Applicants have amended Claim 26 by replacing the term “boracic” with “boric”. Applicants have also replaced the term “boracic” with “boric” in Claim 33.

In view of the amendment, Applicants respectfully request the Office withdraw the objection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office rejects Claims 27, 28, and 36 under 35 U.S.C. § 112, second paragraph, asserting that the term “comprising” was vague and indefinite.

Applicants respectfully traverse. However, in an effort to expedite prosecution and not in acquiescence to the rejections, Applicants have amended Claims 27 and 28 by replacing each occurrence of the term “comprising” with the phrase “consisting essentially of” to recite the number of carbon atoms forming the hydrocarbons.

Applicants have amended Claim 36 by replacing the term “comprising” with the phrase “is selected from” to recite the element of at least one hydrocarbon solvent.

For at least these reasons, Applicants respectfully request the Office withdraw the rejections under 35 U.S.C. § 112, second paragraph.

Claim Rejections Under 35 U.S.C. § 103(a) over Kawabe et al. (U.S. Patent No. 5,763,652) in view of Susumu et al. (JP10059895 translated version)

The Office rejects Claims 20-33 and 41-42 under 35 U.S.C. § 103(a) as being unpatentable over Kawabe et al. (U.S. Patent No. 5,763,652) in view of Susumu et al. (JP10059895 translated version) (Office Action, page 4). The Office alleges that Kawabe et al. teach a process for producing α -hydroxycarboxylic acid by hydrolyzing an α -nitrile compound in the presence of an acidic acid, water, and an inert solvent such as hexane, benzene, xylene, toluene, and other aromatic hydrocarbons, and mixtures thereof (see Office Action, pages 4-5). The Office recognizes the lack of any teaching of a reaction mixture containing less than 10% by weight of an organic solvent.

The Office alleges that Susumu et al. teach a process for producing an optically active 4-phenyl mandelic acid by reacting 4-phenyl benzaldehyde. The Office alleges that during the process a nitrile compound is formed and a solvent system including ethyl acetate, toluene, an acetic acid, methanol, ethanol, water, or a mixture thereof at 0.5 to 5 weight percent to the aldehyde derivative can be used (see Office Action, page 5).

The Office thus concludes that it would have been obvious for one skilled in the art to incorporate the organic solvent weight percent taught by Susumu et al. into the process taught by Kawabe et al., and to optimize the organic solvent system by routine experimentation to obtain Applicants' claimed invention.

Applicants respectfully traverse.

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art reference . . . must teach or suggest all claim limitations.” (*MPEP* § 2143 at 2100-124 (2003)).

Kawabe et al. teach that the hydrolysis of a nitrile compound to produce the corresponding carboxylic acid can be carried out in an inert solvent including aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, alcohols, esters, ethers, ketones, and aprotic solvents. (col. 7, line 66 through col. 8, line 11). In Example 3, Kawabe et al. specifically teach the use of “the organic layer obtained in the amide extracting step (iv)” (col. 22, lines 2-3) which layer comprises methyl ethyl ketone (col. 21, lines 55-56), in the hydrolysis step. As admitted by the Office, Kawabe et al. do not teach a reaction mixture comprising less than 10% by weight of an organic solvent (Office Action, page 5).

Susumu et al. teach a process of producing 4-phenyl mandelic acid by reacting 4-phenyl benzaldehyde in a solvent system including ethyl acetate, toluene, an acetic acid, methanol, ethanol, water, or a mixture thereof, in an amount of 0.5 to 5 times the weight of the aldehyde derivative (paragraph [0016]). That is, Susumu et al. teach a reaction mixture comprising 50 to 500 weight percent solvent to aldehyde derivative. Susumu et al. do not specifically teach the amount of organic solvent other than a hydrocarbon solvent in the hydrolysis reaction mixture. As disclosed by Susumu et al., in the process of producing 4-phenyl mandelic acid from 4-phenylbenzaldehyde, the intermediate α -nitrile compound is not isolated prior to the hydrolysis reaction step. Thus, solvents, including the organic solvents, used to form the intermediate α -nitrile remain in the hydrolysis reaction mixture.

Applicants’ independent Claim 20 recites a method of hydrolyzing an optically pure cyanohydrin to its corresponding α -hydroxycarboxylic acid in a reaction mixture comprising the optically pure cyanohydrin, water, at least one mineral acid that catalyzes the hydrolysis, and at

least one hydrocarbon solvent, wherein the reaction mixture comprises less than 10% by weight of an organic solvent other than the at least one hydrocarbon solvent. Applicants' method is directed to producing α -hydroxycarboxylic acids having high carboxylic acid purity and high optical purity (*see for example*, page 33, paragraph 3; page 44, paragraph 4 - page 45, paragraph 1). Kawabe et al. disclose a process for producing an α -hydroxycarboxylic acid by hydrolyzing an α -nitrile compound without reference to the carboxylic acid purity or optical purity of the α -hydroxycarboxylic acid (*see for example*, col. 2, lines 43-49; col. 6, lines 33-40). Susumu et al. disclose a method for producing a mandelic acid derivative having high purity (abstract) where high purity is determined by HPLC, and therefore represents carboxylic acid purity (paragraphs [0028] - [0035]). Neither Kawabe et al. nor Susumu et al. teach that optical purity is a parameter to be optimized, or that the conditions of the hydrolysis reaction can impact the optical purity of the α -hydroxycarboxylic acid produced. To optimize a particular parameter by routine experimentation, the parameter must first be recognized as a results-effective variable (*see MPEP* § 2144.05 II.B at 2100-138 (2003)). Since neither Kawabe et al. nor Susumu et al. disclose optical purity as a parameter, neither Kawabe et al. nor Susumu et al. recognized optical purity as being a results-effective variable. Thus, there is no motivation to modify that aspect of the claimed invention. Moreover, without even this recognition, there cannot be any expectation of success. Therefore, there is no basis for the Office's allegation that one skilled in the art could optimize the solvent systems disclosed by Kawabe et al. and Susumu et al. to derive the reaction mixture recited in Applicants' Claim 20.

Furthermore, neither Kawabe et al. nor Susumu et al. teach or suggest that the components of the solvent system or the relative amounts of the components of the solvent system can impact the yield or purity of α -hydroxycarboxylic acid. As set forth above, the

reaction mixture of the claimed invention comprises a hydrocarbon solvent. In Table 1, Applicants demonstrate that the presence of a hydrocarbon solvent in the reaction mixture results in improved yield, purity of carboxylic acid, and optical purity of the resulting α -hydroxycarboxylic acid (*for example*, compare Control 1 to Examples 1-4 in Table 1). Neither Kawabe et al. or Susumu et al. teach or suggest that the presence of a hydrocarbon solvent is a results-effective variable. For the same reasons, these references cannot provide a motivation or expectation of success regarding this aspect of the invention.

Applicants further point out that optimizing a method of hydrolyzing a cyanohydrin to produce an α -hydroxycarboxylic acid with high yield and purity of the carboxylic acid is not the same as optimizing a method of hydrolyzing a cyanohydrin to produce an α -hydroxycarboxylic acid having high optical purity with high yield and purity of the carboxylic acid. In Table 1, the Applicants disclose the yield, carboxylic acid purity, and optical purity of (R)-2-chloromandelic acid produced upon hydrolysis of (R)-2-chloromandelonitrile in various weight ratios of hydrocarbon solvents to cyanohydrin. Comparing examples 1 and 2, an increased toluene weight ratio in the reaction mixture results in increased carboxylic acid purity and optical purity, but with a decreased yield. In Table 4, the Applicants disclose the yield, HPLC purity (% carboxylic acid), and the optical purity (% e.e) of the α -hydroxycarboxylic acid ((R)-2-chloromandelic acid) produced for various reaction conditions. As demonstrated, reaction conditions that optimize the yield and HPLC purity of (R)-2-chloromandelic acid do not necessarily optimize the optical purity of the (R)-2-chloromandelic acid. For example, considering control example 1 and control example 2 of Table 4, increasing the molar ratio of 35% HCl from 3 to 20, reducing the reaction temperature from 100 °C to 50 °C, and increasing the reaction time from 2 hours to 12

hours, results in an increase in HPLC purity and optical purity of (R)-2-chloromandelic acid, but with a decrease in the yield of (R)-2-chloromandelic acid.

The foregoing arguments are applied to independent Claim 33.

For at least these reasons, Applicants' independent Claims 20 and 33 are non-obvious under 35 U.S.C. § 103(a) over Kawabe et al. in view of Susumu, et al.

Since independent Claims 20 and 33 are herein shown to be non-obvious over Kawabe et al. in view of Susumu et al., dependent Claims 21-32, and 41-42, which depend from independent Claims 20 and 33, are similarly shown to be non-obvious over Kawabe et al. in view of Susumu et al. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is also non-obvious.).

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) over Kawabe et al. in view of Susumu, et al.

Claim Rejections under 35 U.S.C. § 103(a) over Susumu et al. (JP10059895 translated version)

The Office rejects Claims 34-40 under 35 U.S.C. § 103(a) as being unpatentable over Susumu et al. (JP10059895 translated version) (see Office Action, page 6).

The Office alleges that Susumu et al. teach a process of crystallizing 4-phenyl mandelic acid using ethyl acetate, toluene, an acetic acid, methanol, ethanol, and water or a mixture of the foregoing at 0.5 to 5 weight percent to the aldehyde derivative. (see Office Action, page 7). The Office acknowledges that the ratio of the volume of the aqueous solution to that of the non-miscible organic solvent ranges from 1 : 0.05 to 1 : 1, the 0.5 °C/min cooling rate during crystallization, and the crystalline packing density of 0.5 g/cm³ as recited by the Applicants is not taught by Susumu et al. However, the Office considers the chemical process ranges recited by the Applicants to be within those that would be determined by one of ordinary skill in the art

during process optimization (see Office Action, page 7). Furthermore, as a physical property of a chemical compound, the Office does not regard the packing density of 0.5 g/cm^3 of the crystalline optically active α -hydroxycarboxylic acid as novel (see Office Action, page 8).

Applicants respectfully traverse the Office's rejections over Susumu et al.

Susumu et al. disclose a method for producing mandelic acid derivatives having high HPLC purity with high yield (abstract). Susumu et al. do not address the synthesis or crystallization of mandelic acid derivatives having high optical purity. Susumu et al. do not recognize optical purity as being a results-effective variable and therefore there can be no motivation or likelihood of success in any "optimization" of any recited condition.

Applicants' independent Claim 34 is directed to a method of crystallizing an optically pure α -hydroxycarboxylic acid in an aqueous solution. As shown in Table 5 of the specification, the presence of a non-miscible organic solvent such as toluene or p-xylene, the final temperature of the aqueous solution, and the cooling rate can be selected to obtain an α -hydroxycarboxylic acid such as (R)-2-chloromandelic acid having high optical purity and packing density. Susumu et al. merely describe a method for isolating 4-phenyl mandelic acid from a reaction mixture by crystallization. The invention of Susumu et al. is directed to a method for manufacturing mandelic acid derivatives in a simple industrial process. (paragraph [0003]). Susumu et al. do not teach or suggest that the method for isolating 4-phenyl mandelic acid addresses the optical purity of mandelic acid derivatives, or that any reaction conditions can impact the optical purity of the resulting mandelic acid derivatives. Susumu et al. fail to provide any suggestion that any of the variables recited by the Applicants are relevant toward obtaining optically pure α -hydroxycarboxylic acids.

For at least these reasons, Applicants' independent Claim 34 is non-obvious under 35 U.S.C. § 103(a) over Susumu et al.

Since independent Claim 34 is herein shown to be non-obvious over Susumu et al., dependent Claims 35-40 which depend from independent Claim 34 are herein shown to be non-obvious over Susumu et al. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is also non-obvious.).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 34-42 under 35 U.S.C. § 103(a) over Susumu et al. (JP10059895 translated version).

CONCLUSION

In view of the foregoing Amendment and Remarks, Applicants respectfully submit that the claimed invention is not rendered obvious in view of the prior art references cited against this application. Applicants therefore request the Office's reconsideration of the application and the timely allowance of the claims.

Please grant any extensions of time required to enter this response.

If this response does not put the claims in condition for allowance, Applicants earnestly request the Examiner to contact their representative at 650.849.6661.

If there is any additional fee due in connection with the filing of this Amendment, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

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